WHO-PQTm SCIENTIFIC DISCUSSION

This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	Insulatard [1]
Manufacturer of Prequalified Product:	Novo Nordisk A/S, Novo Alle, 2880 Bagsværd, Denmark
Active Pharmaceutical Ingredient (API):	Insulin human
Pharmaco-therapeutic group (ATC Codes):	A10AC01 insulin (human)
WHO recommended therapeutic indication:	Diabetes mellitus

1 Introduction

Insulatard (insulin human) is manufactured by recombinant DNA technology in Saccharomyces cerevisiae. The active substance of Insulatard, human insulin (rDNA) complies with Ph.Eur. monograph 1999:838 with additional tests as follows:

Identification by amino acid composition

Nitrogen content

Total viable count (CFU/g)

DNA content.

The prequalification of this product by the WHO Prequalification Team: Medicines (PQTm) is based on the approval by a stringent regulatory authority (SRA), namely "European Medicines Agency" (https://www.ema.europa.eu/en) in line with the "WHO Guidelines on submission of documentation for the pilot procedure for prequalification of human insulin approved by stringent regulatory authorities – abridged assessment pathway"[2].

Hence, no assessment of the data underlying this approval has been undertaken within PQTm. However, according to the above-mentioned guidelines, WHO requested additional data for the safe use of the product in regions relevant for prequalified products and this information is included in this section of the WHOPAR.

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

[2] https://extranet.who.int/pqweb/sites/default/files/documents/03_GLs_Submission_SBP_Pilot_AbridgedPathway_insulinFeb2020.pdf

2 Assessment of Quality

Product packaging and shipping

The assessment of the packaging and shipping of the product has been done according to the principles laid down in the WHO guidelines on the international packaging and shipping of vaccines (WHO/IVB/05.23), partially applicable also to biotherapeutics.

The Applicant provided operational qualification tests of transport units executed under abnormal and extreme ambient temperatures and time conditions. The temperature tests simulated worst-case situations where the product is outside cold storage conditions for long time.

Furthermore, the applicant provided performance qualification testing of the product's transport by air and sea freight. The tests were executed considering the worst-case scenario (most challenging routes considering climate zones, duration and handling). Three consecutive field tests were performed by air and sea freight with temperature loggers (continuous monitoring) under real time and temperature conditions.

The temperature of each shipment was kept between 2 – 8 °C when transported in cold chain. During handling steps where the products were exposed to ambient temperatures, temperatures outside 2 – 8 °C were seen, however, these were within the allowed temperature excursions for the product (Product Specific Requirements (PSRs) based on stability data).

The applicant also provided evidence that the transport of product is performed according to GDP requirements and that the shipments are continuously monitored by calibrated temperature logging devices from the moment the pallets are dispatched until they are received at their final destination. Furthermore, data from the temperature loggers are evaluated before release. Any deviations from the allowed temperatures will be handled in a deviation report according to applicant's procedures.

Arrangements for handling complaints and product recalls

The procedure for handling product quality complaints and product recalls submitted by the applicant provides details, among others, on the product defects/serious quality issues definition, investigation process, process of recalls, established timelines for recall notification to National Medicines Regulatory Authorities and WHO, recall arrangements and actions to put in place at the distribution level as well as description of the annual mock-recall.

The applicant confirmed that the responsibilities for handling of complaints and recalls will also be clearly defined in the agreements or contracts between the manufacturer and relevant third parties.

Stability of the product

The approved shelf-life for Insulatard is 30 months at 5°C and in-use storage condition of 4 weeks at 30°C for the vial presentation.

The Applicant proposed an additional optional storage time before use (4 weeks below 30°C) to meet the needs of countries with limited access to refrigeration. This optional storage condition is supported by long-term stability data of product's batches which were representative of the commercial product. To account for the storage period of 4 weeks below 30°C before use, Novo Nordisk proposed to shorten the maximal storage time before use with 6 months from 30 months to 24 months. The stability profile after a storage period of 24 months at 2-8°C was included as a baseline for the evaluation of the storage at increased temperature (below 30°C) for an additional 4 weeks. The

additional storage option before use (4 weeks below 30°C) is therefore applicable if there are 6 months or more until expiry.

Conclusion: The quality part of the dossier is accepted.

Pharmacovigilance - WHO PREQUALIFICATION-SPECIFIC ADDENDUM to the RMP

WHO assessed the latest SRA-approved Risk-Management Plan (RMP) and post-marketing safety reports together with a WHO PQ-specific addendum to the RMP according to the structure detailed on the WHO-PQT website[3]

The WHO-prequalification-specific addendum to the RMP is reported below.

Conclusion: The pharmacovigilance part of the dossier is accepted.

[3] https://extranet.who.int/pqweb/sites/default/files/documents/RMP_AddStructureDec2019-2.pdf

Risk Management Plan Addendum for WHO Pre-Qualification

Human Insulin Products: Actrapid® and Insulatard®

QPPV or delegate name and signature:
Please refer to the last page

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1 General information

1.1 Overview

This addendum to the Novo Nordisk human insulin (HI) risk management plan (RMP) supports the WHO pre-qualification application for Novo Nordisk HI products: Actrapid® and Insulatard®.

Actrapid® is a fast-acting HI and Insulatard® is an intermediate-acting HI with a long duration of action. Both are approved for the treatment of diabetes mellitus.

The first marketing authorisations for these products were received on 08 Jul 1988. Both products have been approved and launched in more than 130 countries over a period spanning more than 30 years. Consistent with such extensive post-marketing experience, the shared safety profile of Actrapid® and Insulatard® is established and well characterised, with hypoglycaemia, immunological/hypersensitivity reactions, and mix-ups between insulin products constituting the primary risks to patients. Notably, these risks are common to insulin products as a class.

The current RMP (Version 3.1) for Novo Nordisk HI products was approved by the European Medicines Agency (EMA; procedure numbers EMEA/H/C/000424/WS1582 and EMEA/H/C000441/WS1582 for Actrapid® and Insulatard®, respectively) in July 2019. In alignment with an established safety profile informed by several decades of post-marketing safety data, all important risks are considered fully characterised and appropriately managed through routine pharmacovigilance activities, with no further risk management required.

Additionally, EMA assessment of the current RMP (Version 3.1) in a procedure for assessment of Actrapid® and Insulatard® under Article 58 of Regulation EC no. 726/2004 (concerning evaluation of medicines for use outside the EU; procedure number EMEA/H/W/005779 and EMEA/H/W/005780) was recently completed in April 2022, resulting in a Positive Opinion.

1.2 Product information and posology

Actrapid® and Insulatard® contain the same active ingredient, although the formulations and pharmacodynamic profiles differ. Actrapid® is a human insulin solution designed for a rapid onset of action. Insulatard® is a neutral suspension of isophane insulin crystals formulated for a long duration of action.

Dosage of Actrapid® and Insulatard® is in accordance with the individual patient's needs but is typically between 0.3 and 1.0 IU/kg/day. Blood glucose monitoring is recommended to achieve optimal glycaemic control. As with all insulin products, adjustment of the dose may be necessary if patients undertake increased physical activity, change their usual diet or during any concomitant illness. Table 1-1 presents an overview of the general product information for Actrapid® and Insulatard®.

Table 1-1 Product information for Actrapid® and Insulatard®

Product names	Actrapid® and Insulatard®
Pharmaceutical form	• 10 mL vial (100 international units/ml) • 3 mL Penfill® (100 international units/ml) cartridges for Novo Nordisk insulin pen injectors.
Method of administration	• Subcutaneous (Actrapid® and Insulatard®) • Intravenous (Actrapid® vials; only to be administered by health care professionals)
Indication	Treatment of diabetes mellitus
Posology	*Actrapid®* Actrapid® dosing is individual and determined in accordance with the needs of the patient. It can be used before a meal or a snack. The total daily individual insulin requirement is usually between 0.3 and 1.0 international unit/kg/day. Adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during any concomitant illness. Special populations: *Elderly (≥ 65 years old)* Actrapid® can be used in elderly patients. In elderly patients, glucose monitoring should be intensified, and the insulin dose adjusted on an individual basis. *Renal and hepatic impairment* Renal or hepatic impairment may reduce the patient's insulin requirements. In patients with renal or hepatic impairment, glucose monitoring should be intensified, and the human insulin dose adjusted on an individual basis. *Paediatric population* Actrapid® can be used in children and adolescents. *Insulatard®* Insulatard® dosing is individual and determined in accordance with the needs of the patient. The physician determines whether one or several daily injections are necessary. Insulatard® may be given at meals. Blood glucose monitoring is recommended to achieve optimal glycaemic control.

	The total daily individual insulin requirement is usually between 0.3 and 1.0 international unit/kg/day. Adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during any concomitant illness. Special populations: *Elderly (≥ 65 years old)* Insulatard® can be used in elderly patients. In elderly patients, glucose monitoring should be intensified, and the insulin dose adjusted on an individual basis. *Renal and hepatic impairment* Renal or hepatic impairment may reduce the patient's insulin requirements. In patients with renal or hepatic impairment, glucose monitoring should be intensified, and the human insulin dose adjusted on an individual basis. *Paediatric population* Insulatard® can be used in children and adolescents
First marketing authorisation	08 Jul 1988
Years of post-marketing experience	>30 years

2 Safety concerns

The safety profiles of Actrapid® and Insulatard® are well established, with more than 30 years of post-marketing experience, based on worldwide safety data from more than 130 countries, including low- and middle-income countries. Consequently, the risk management plan of these products (Version 3.1; endorsed by the EMA in procedures EMEA/H/C/000424/WS1582 and EMEA/H/C000441/WS1582 for Actrapid® and Insulatard®, respectively) does not include any risks, as all risks are considered sufficiently characterised and appropriately managed through routine pharmacovigilance activities.

A summary of the key safety concerns from the reference safety information (RSI) for Actrapid® and Insulatard® are presented in Table 2-1.The risks presented in Table 2-1 are the important identified risks, characterised and presented in periodic aggregate reporting, as well as additional risks included in the RSI. In accordance with GVP module V (EMA/838713/2011 Rev 2), these risks are not presently included in the safety specification of the current RMP as these risks are considered to be fully characterised and appropriately managed by routine pharmacovigilance activities (i.e., there are no outstanding additional pharmacovigilance activities and/or additional risk minimisation activities beyond the routine) or are non-important.

Table 2-1 Summary of the key safety concerns for Actrapid® and Insulatard®.

Risk	Pharmacovigilance activities	Risk minimisation measures	Endorsed EMA procedure for removal of the risk from RMP
Important identified risks			
Hypoglycaemia	*Routine pharmacovigilance activities:* Routine pharmacovigilance Aggregate reporting (PSURs/PBRERs) *Additional pharmacovigilance activities:* None	*Routine risk minimisation measures:* Dosing recommendations and precautions are included in EU SmPC Sections 4.2 and 4.4, respectively. Furthermore, recommendations (including the need for close glucose monitoring and the potential need for dose adjustments) for transfer from other insulins to Actrapid® or Insulatard® are included in Section 4.2 of the EU SmPCs. The risk of hypoglycaemia is additionally described in Section 4.8 of the EU SmPC. Hypoglycaemia associated with overdose for insulin is also included in Section 4.9 of the EU SmPC. Section 2 of the EU product leaflet (PL) describes conditions where hypoglycaemia may be a relevant concern. Similarly, Section 4 of the EU PL provides information and guidance concerning the risk of "low blood sugar (hypoglycaemia)". *Additional risk minimisation measures:* None	*RMP Version:* Version 2.2 26 Oct 2017 *EMA Procedure:* EMEA/H/C/000424/WS1197 (Actrapid®) EMEA/H/C/000441/WS1197 (Insulatard®)
Anaphylactic reactions	*Routine pharmacovigilance activities:* Routine pharmacovigilance Aggregate reporting (PSURs/PBRERs)	*Routine risk minimisation measures:* A contraindication related to hypersensitivity to the active substance or any of the excipients is included in Section 4.3 of the EU SmPC.	*RMP Version:* Version 2.2 26 Oct 2017 *EMA Procedure:*

Risk	Pharmacovigilance activities	Risk minimisation measures	Endorsed EMA procedure for removal of the risk from RMP
	Additional pharmacovigilance activities: None	Furthermore, allergic reactions are addressed in Section 4.8 of the EU SmPC. Sections 2 and 4 of the EU PL provide information and guidance concerning the risk of "serious allergic reactions". *Additional risk minimisation measures:* None	EMEA/H/C/000424/WS1197 (Actrapid®) EMEA/H/C/000441/WS1197 (Insulatard®)
Medication errors (including human error related medication errors)	*Routine pharmacovigilance activities:* Routine pharmacovigilance Aggregate reporting (PSURs/PBRERs) *Additional pharmacovigilance activities:* None	*Routine risk minimisation measures:* Instructions for avoidance of medication errors are reflected in Section 4.4 of the EU SmPC. Special precautions for disposal and handling of needles, syringes and Penfill® cartridges are described in Section 6.6 of the EU SmPC. Product differentiation strategy includes trade names, label text, colour branding of the carton, container label and cartridge holder *Additional risk minimisation measures:* None	*RMP Version:* Version 3.1 11 Jul 2019 *EMA Procedure:* EMEA/H/C/000424/WS1582 (Actrapid®) EMEA/H/C/000441/WS1582 (Insulatard®)
Additional risks included in the RSI			
Urticaria, rash.	*Routine pharmacovigilance activities:* Routine pharmacovigilance Aggregate reporting (PSURs/PBRERs) *Additional pharmacovigilance activities:*	*Routine risk minimisation measures:* Injection site reactions, and related recommendations, are discussed in Section 4.4.in the EU SmPC. Emphasis is placed on rotation of the injection site to reduce risk of developing these reactions.	*RMP Version:* Version 2.2 26 Oct 2017 *EMA Procedure:* EMEA/H/C/000424/WS1197 (Actrapid®) EMEA/H/C/000441/WS1197 (Insulatard®)

Risk	Pharmacovigilance activities	Risk minimisation measures	Endorsed EMA procedure for removal of the risk from RMP
	None	Section 4.8 (Undesirable effects) of the EU SmPC indicates these kinds of skin reactions can occur when insulin therapy is initiated but that it is typically transient. Local allergic reactions are also discussed in Section 4 of the EU PL as part of section entitled "list of other side effects". Contact with a physician is recommended if the reaction is not transient. *Additional risk minimisation measures:* None	
Peripheral neuropathy (painful neuropathy).	*Routine pharmacovigilance activities:* Routine pharmacovigilance Aggregate reporting (PSURs/PBRERs) *Additional pharmacovigilance activities:* None	*Routine risk minimisation measures:* Section 4.8 (Undesirable effects) of the EU SmPC indicates rapid, reversible, peripheral neuropathy can occur when insulin therapy is initiated and there is rapid improvement in blood glucose control. Painful neuropathy (pain due to nerve damage) is also described in Section 4 of the EU PL as part of section entitled "list of other side effects". *Additional risk minimisation measures:* None	*RMP Version:* Version 2.2 26 Oct 2017 *EMA Procedure:* EMEA/H/C/000424/WS1197 (Actrapid®) EMEA/H/C/000441/WS1197 (Insulatard®)
Diabetic retinopathy,	*Routine pharmacovigilance activities:* Routine pharmacovigilance	*Routine risk minimisation measures:*	*RMP Version:* Version 2.2 26 Oct 2017 *EMA Procedure:*

Risk	**Pharmacovigilance activities**	**Risk minimisation measures**	**Endorsed EMA procedure for removal of the risk from RMP**
	Aggregate reporting (PSURs/PBRERs) *Additional pharmacovigilance activities:* None	Section 4.8 (Undesirable effects) of the EU SmPC indicates diabetic retinopathy can temporarily worsen with abrupt improvement in blood glucose control. Long-term control of blood glucose is also stated to decrease the progression of diabetic retinopathy Diabetic retinopathy is also discussed in Section 4 of the EU PL as part of section entitled "list of other side effects". Contact with a physician is recommended if existing retinopathy worsens with rapid improvements in blood glucose levels. *Additional risk minimisation measures:* None	EMEA/H/C/000424/WS1197 (Actrapid®) EMEA/H/C/000441/WS1197 (Insulatard®)
Lipodystrophy	*Routine pharmacovigilance activities:* Routine pharmacovigilance Aggregate reporting (PSURs/PBRERs) *Additional pharmacovigilance activities:* None	*Routine risk minimisation measures:* A recommendation to always rotate injection sites within the same region to reduce the risk of lipodystrophy is included in Section 4.2, and reinforced in Sections 4.4, and 4.8 of the EU SmPC.	*RMP Version:* Version 2.2 26 Oct 2017 *EMA Procedure:* EMEA/H/C/000424/WS1197 (Actrapid®) EMEA/H/C/000441/WS1197 (Insulatard®)

Risk	Pharmacovigilance activities	Risk minimisation measures	Endorsed EMA procedure for removal of the risk from RMP
		Skin and subcutaneous disorders, including lipodystrophy, are discussed in more detail in Sections 4.4 and 4.8.in the EU SmPC. The impact on insulin absorption and glycaemic control are emphasized. Blood glucose monitoring is recommended in Section 4.4 after switching from an affected site to an unaffected area and dose adjustment may be required. Skin changes at the injection site are also discussed in Section 4 of the EU PL as part of section entitled "list of other side effects. It is recommended to change the injection site with each injection to prevent related skin changes. *Additional risk minimisation measures:* None	
Injection site reactions	*Routine pharmacovigilance activities:* Routine pharmacovigilance Aggregate reporting (PSURs/PBRERs) *Additional pharmacovigilance activities:* None	*Routine risk minimisation measures:* Injection site reactions, and related recommendations, are discussed in Section 4.4.in the EU SmPC. Emphasis is placed on rotation of the injection site to reduce risk of developing these reactions. Section 4.8 (Undesirable effects) of the EU SmPC indicates these kinds of reactions can occur when insulin therapy is initiated but that it is typically transient.	*RMP Version:* Version 2.2 26 Oct 2017 *EMA Procedure:* EMEA/H/C/000424/WS1197 (Actrapid®) EMEA/H/C/000441/WS1197 (Insulatard®)

Risk	Pharmacovigilance activities	Risk minimisation measures	Endorsed EMA procedure for removal of the risk from RMP
		Local allergic reactions are also discussed in section 4 of the EU PL as part of section entitled "list of other side effects". Contact with a physician is recommended if the reaction is not transient. *Additional risk minimisation measures:* None	
Oedema	*Routine pharmacovigilance activities:* Routine pharmacovigilance Aggregate reporting (PSURs/PBRERs) *Additional pharmacovigilance activities:* None	*Routine risk minimisation measures:* Injection site reactions (including swelling), and related recommendations, are discussed in Section 4.4.in the EU SmPC. Emphasis is placed on rotation of the injection site to reduce risk of developing these reactions. Section 4.8 (Undesirable effects) of the EU SmPC indicates swelling at the injection site can occur when insulin therapy is initiated but that it is typically transient. Local allergic reactions, including oedema and swelling, are also discussed in section 4 of the EU PL as part of section entitled "list of other side effects". Contact with a physician is recommended if the reaction is not transient. Swollen joints due to water retention are also included as a possible side effect in section 4 of the EU PL. This is described as typically transient and contact with a physician is encouraged if it persists.	*RMP Version:* Version 2.2 26 Oct 2017 *EMA Procedure:* EMEA/H/C/000424/WS1197 (Actrapid®) EMEA/H/C/000441/WS1197 (Insulatard®)

Risk	Pharmacovigilance activities	Risk minimisation measures	Endorsed EMA procedure for removal of the risk from RMP
		Additional risk minimisation measures: None	

Abbreviations: EMA = European Medicines Agency; EU = European Union; PBRER = Periodic benefit-risk evaluation report; PL = product leaflet; PSUR = periodic safety update report; RMP = risk management plan; RSI = reference safety information; SmPC = summary of product characteristics.

Novo Nordisk acknowledges that healthcare settings and infrastructure may vary between countries, and continuously evaluates the adequacy of the safety concerns via routine pharmacovigilance (PV), and traceability of the product at a national level. Despite the variation in healthcare setting and infrastructure, Novo Nordisk's PV system has been developed to monitor the safety concern and PV activities at a national or regional level (where one affiliate manages the PV activities for several neighbouring countries). This system has been used effectively to ensure patient safety for more than thirty years for all Novo Nordisk products, including Actrapid® and Insulatard®.

3 Pharmacovigilance activities

Novo Nordisk's global organisation is split into regions and affiliates, with national affiliates present in most countries, and regional affiliates where one affiliate ensures PV compliance for several regional states. The national/regional affiliates are responsible for monitoring local PV legislation and informing the current national requirements. No additional PV activities are currently deemed necessary on a national level for Novo Nordisk's HI.

Current monitoring is performed by means of quarterly signal detection and through the global periodic safety update reports (PSURs). Signal detection involves the examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, scientific literature information or other data sources to detect new risks or changes to existing risks of a product. Any new safety concern that may arise is followed up with appropriate actions such as introduction of new risk minimisation measures, if needed.

Additionally, signals validated by Novo Nordisk are presented in detail in PSURs. The routine PSURs will be prepared in accordance with the national requirements for submission to the national health authorities in these countries.

The requirement of any additional PV activities will be assessed through routine surveillance, factoring in the local specificities such as epidemiology, healthcare infrastructure, clinical practice, social, economic, and other factors.

4 Risk minimisation measures

A well-characterised safety profile has emerged for Actrapid® and Insulatard® from an extensive worldwide array of safety data encompassing more than 30 years of post-marketing experience, based on worldwide safety data from more than 130 countries. Consistent with a safety profile of this level of maturity, all important risks for Novo Nordisk HI products are considered fully characterised and appropriately managed, without the requirement for further risk management as of the current EMA-endorsed RMP (Version 3.1; procedure numbers EMEA/H/C/000424/WS1582 and EMEA/H/C000441/WS1582 for Actrapid® and Insulatard®, respectively).

Specifically, only routine risk minimisation measures in the form of the guidance contained in the summary of product characteristics (SmPC) and the corresponding product leaflets (PLs) are presently incorporated globally into standard clinical practice relating to Actrapid® and Insulatard®. No additional risk minimisation measures (including non-promotional educational materials, etc.) are presently active in any country for any risks, including the important identified risks specified in Table 2-1. As there has been a lengthy presence on the global market and an extensive exposure, spread over numerous countries (including low and middle-income countries), to the appropriate patient populations for both Actrapid® and Insulatard®, there is a high degree of familiarity amongst health care professionals (HCPs) in all marketed countries in relation to the safety concerns associated with the use of these insulins. The distribution of the corresponding SmPCs and PLs for both Actrapid® and Insulatard® is in accordance with all national requirements, with additional access to SmPCs, and related product information available online[4]. In connection with any new applications for marketing authorisations in any additional countries or with any updates or other conditions for the products that should require non-promotional educational materials, such non-promotional educational materials will be provided in accordance with national requirements.

5 Product traceability

Novo Nordisk has adequate global batch tracing systems in place to enable a clear overview of batch linkages within and outside Novo Nordisk. Identification of any particular batch of product can be facilitated through this system. Specifically, where appropriate and possible, batch numbers from product labels are collected in association with adverse event reporting.

6 Summary

Actrapid® and Insulatard® have well characterised safety profiles, informed by more than 30 years of post-marketing experience from extensive worldwide sources. Consequently, all risks in the RMP for HI products are considered sufficiently characterised and appropriately managed by routine pharmacovigilance activities, with no requirement for risk minimisation measures.

In summary, Novo Nordisk considers the benefit risk relationship for Actrapid® and Insulatard® favourable to all patients with diabetes worldwide.

[1] https://www.ema.europa.eu/en/documents/product-information/actrapid-epar-product-information_en.pdf and https://www.ema.europa.eu/documents/product-information/insulatard-epar-product-information_en.pdf